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OF
THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

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Portrait by Paul Trebilcock

W. G. MacCallum

UNIV. OF MICH.

THE PRESENTATION OF THE PORTRAIT OF DR. W. G. MACCALLUM TO THE JOHNS HOPKINS UNIVERSITY

ROBERT A. LAMBERT

Mr. President, Ladies, and Gentlemen:

I come before you as the spokesman for a group of men and women who have had the good fortune to have been the pupils of a great inspiring teacher, and who are happy today in the opportunity, which this occasion affords, to give public expression of their regard for him.

Dr. MacCallum is so well known to most of you in this University family gathering that a biographical note is hardly necessary. However, for the benefit of those who may not know him, I shall sketch briefly his academic career. A bachelor of arts from the University of Toronto, 1894, doctor of medicine from Johns Hopkins, 1897, holder of various subordinate posts of ascending rank in Johns Hopkins Hospital and Medical School from 1898 to 1907, Dr. MacCallum attained a full professorship in 1908 when the chair of pathological physiology was created for him at Johns Hopkins. The following year he accepted the headship of the department of pathology at Columbia University, succeeding Dr. T. M. Prudden, one of America's pioneer pathologists. After eight years at Columbia, that is in 1917, he returned to Baltimore as successor to Dr. Welch in the Baxley Professorship in Pathology at Johns Hopkins—a post which he still holds. If this record suggests that Dr. MacCallum must be considerably older than he looks, I may explain that he attained a professorship at an exceptionally early age, so early that some of his pupils, I suspect, are older than he. This will give you a hint as to why his pupils did not think it discreet to wait until he was three score and ten to do him honor.

During his twenty-two years' professorship at Johns Hopkins and Columbia Dr. MacCallum has had as staff assistants and graduate workers in his department nearly one hundred pupils, most of whom are now occupying academic posts in some two score widely scattered institutions.

In attempting to interpret the feeling of this large group toward Dr. MacCallum, and particularly the sense of affectionate gratitude which has prompted this manifestation today, I am quite naturally tempted to fall back on an analysis of my own reactions. While I came to Dr. MacCallum more ignorant than most of the pupils who followed me, I believe my case is reasonably representative. In thinking over what I got from my nine years' relationship that began, I may remark, here at Johns Hopkins in 1908 and continued through Dr. MacCallum's eight years service at Columbia, I am inclined to say that my first conscious gain was a more critical point of view, a questioning attitude toward the numerous problems of medicine. Arriving full of the assurance of the fresh graduate, I acquired a wholesome disrespect for certainty and orthodoxy in science. I also got a new conception of pathology in that I was brought to realize that it is not a well defined discipline, a compilation of static factual knowledge, distinct from physiology and anatomy on the one hand and from clinical medicine on the other, as it had seemed to me in the regular undergraduate course, but that, as Dr. MacCallum himself has so aptly put it, pathology and clinical medicine are essentially the same thing viewed from slightly different angles.

In presenting pathology thus broadly as a science of disease without any definite boundaries, Dr. MacCallum anticipated the present tendency toward a breaking down of the barriers between the various medical and biological sciences. Through emphasis on etiology and the clinical significance of pathological changes, by stressing the relation between functional and anatomical disturbances, and by constantly focussing attention upon the possibilities of experiment in solving the riddles of disease, Dr. MacCallum put life and meaning into the dead facts of pathological anatomy. His conception of pathology is admirably set forth in his textbook, the building and launching of which I had the opportunity to see, and I venture the opinion that few medical texts have so perfectly filled a recognized need.

To young medical graduates interested in teaching and investigation as a career, Dr. MacCallum made pathology present a very strong appeal, and, as might have been expected, many of the pupils he attracted have found their training with him a stepping-stone to

success in clinical medicine. While I have no doubt that he himself has been disappointed at times in seeing some of his best men leave the laboratory for the lure of the clinic, he will have to grant that the very broadness of his teaching makes a move from pathology to clinical medicine a natural step, and, I might add, a step in the interest of the general good, in view of the wide opportunities which have developed in the field of clinical investigation.

But I do not want to overstress plan and method in interpreting Dr. MacCallum's influence on his pupils. Indeed, I am certain that, as in the case of most great teachers, he influenced his students less through any methodology or conscious effort in direction than through the more intangible effect of his personality upon those about him. No one close to him could fail to be stirred by the spontaneity and brilliance of his ideas—seasoned often with a rare humor—or to be stimulated by his infectious enthusiasm over a new concept or new technique. Every worker in the department was conscious of the fact that he had at his command at all times Dr. MacCallum's aid and counsel, whether in formulating a working hypothesis or in overcoming a difficulty in technique. Dr. MacCallum always seemed to me to be careful, however, not to discourage originality through overhelpfulness. This reminds me of an answer I recently got from a graduate student, a young physician, whom I asked to explain his enthusiasm over a six-month's experience in Dr. MacCallum's department. He began with the remark that he had found in the department of pathology at Johns Hopkins a stimulating freedom to think and work such as he had not experienced in his previous four years' medical course; a discriminating judgment which, I am sure, many other pupils would echo, and which I think contains a part of the secret of Dr. MacCallum's success as a scientific leader.

Time does not permit comment on Dr. MacCallum as an investigator even to the extent of naming his outstanding contributions. I do want to point out, however, that his example as a brilliant, resourceful, and rigidly careful experimenter has been a large factor in the influence he exerted on his pupils. I wish to call special attention to one of his traits which early excited my admiration, namely, his catholicity of interest. In this age of specialization and narrow intensiveness, even more pronounced in the investigative side of

medicine than in the practice of the profession, it is not only refreshing but inspiring to find an investigator who demonstrates, as Dr. MacCallum does so well, the possibility of notable accomplishment in a number of different subjects. Dr. MacCallum has attacked successfully, as many of you know, not only a variety of problems, but problems belonging to what are usually regarded as quite distinct domains—anatomy, parasitology, pathological physiology, as well as pathology and bacteriology. He has shown that, given a sound basic knowledge of a subject, a mastery of technique, and a good critical sense, an investigator may with profit and happiness indulge in a diversity of interests. I am personally indebted to him for encouraging me to broaden my horizon even though this led me ultimately out of the laboratory.

With this very inadequate introduction, I come now to the special purpose of my appearance before you. The pupils of Dr. MacCallum, including, as I have indicated, members of his staff and graduate workers, 1908 to 1930, at Johns Hopkins, Columbia, and again at Johns Hopkins, some months ago resolved, as the result of an informal exchange of ideas, to express in some definite way their esteem, admiration, and affection for him, and it was decided that a portrait would best satisfy this desire. The committee which was formed happily secured the services of the distinguished young artist, Mr. Paul Trebilcock of Chicago, and the portrait, with Dr. MacCallum's gracious submission, was painted. Of the success of Mr. Trebilcock's work, I shall leave you to judge, in the confidence that you will share the committee's enthusiastic satisfaction over it.

And now, Mr. President, on behalf of the pupils of Professor William George MacCallum, I have the honor and pleasure to present to Johns Hopkins University this portrait of their beloved friend and teacher, who happens to be also one of the University's most distinguished sons.

SUBCUTANEOUS NODULES OF THE JUXTA-ARTICULAR TYPE[1, 2]

H. HANFORD HOPKINS

From the Syphilis Division of the Medical Clinic, The Johns Hopkins Hospital, Baltimore, Maryland

Subcutaneous fibroid nodules of the juxta-articular type have attracted a moderate amount of attention since their first full description by Jeanselme (1) in 1901. Interest in them has been limited to two groups of observers; dermatologists, who saw them frequently in yaws and syphilis, and internists, who associated them with rheumatic fever or rheumatoid arthritis. In this country, considerable confusion has been created as to their etiology as a result of papers by Goodman and Young (2) and by Fox (3), who stress syphilis as an etiologic factor, and by Dawson and Boots (4) who feel that they occur in rheumatic fever and rheumatoid arthritis but not in other conditions.

Interest in the general subject of subcutaneous fibroid nodules was first aroused in the third quarter of the nineteenth century when many observers noted their frequent association with rheumatic fever. For a considerable period of time it was thought that they were pathognomonic of that disease, until Fowler (5) and others noted that they sometimes occurred in patients who exhibited no demonstrable signs of rheumatism. In 1884 Fowler reported the case of a white man of thirty-five, with a questionable history of early syphilis ten years before, who had nodules over the extensor surfaces of the forearms near the olecranons, over the tibial tuberosities, and other parts of the body. The patient showed no evidence of rheumatic fever and Fowler remarked that he no longer considered that such nodules were always indicative of rheumatism. Futcher, in 1893, reviewed the

[1] This study has been supported by a grant from the Committee on Research in Syphilis, Inc.

[2] Submitted for publication May 1, 1931.

literature dealing with subcutaneous fibroid nodules and mentioned syphilis as a possible cause in some cases. It was at about this time that dermatologists became interested in the condition. Although credit for calling attention to the so-called juxta-articular type of subcutaneous fibroid nodule has generally been attributed by dermatologists to Lutz (6), a leprologist in Honolulu, who described them in supposed lepers, and also to MacGregor, who almost simultaneously described them independently, it was Jeanselme (7) who crystallized Fowler's departure from current opinion into a new concept by coining the name, juxta-articular nodule, for lesions occurring in the characteristic areas. His first observations were made in Indo-China among a population afflicted with both syphilis and yaws, and his attention was arrested by the curious symmetry, indolence, and painlessness of the lesions, characteristics with which we are familiar today. He at first thought that the juxta-articular nodules he observed were a manifestation of yaws, but it was soon shown that they could be also associated with syphilis, because numerous workers from various parts of the temperate zone where yaws was unknown reported cases of syphilis exhibiting such nodules which disappeared after anti-syphilitic treatment. Jessner (8) has admirably reviewed the literature having to do with the syphilitic subcutaneous fibroid nodule.

Not only have syphilis, yaws and the rheumatic diseases been incriminated as causes of this lesion but numerous other diseases as well. Several authors have reported them as occurring in association with acrodermatitis chronica atrophicans. Ketron (9) reported such a case and his paper included a drawing of the juxta-articular nodules, and also drawings of sections made from the nodules. His description of the histology of the nodules does not differ materially from the descriptions by other workers of nodules associated with syphilis or other diseases. He classed them as fibroids. In 1923 Gray (10) reported the case of a young white woman of 26, suffering with diffuse scleroderma, who exhibited numerous subcutaneous fibroid nodules in the characteristic juxta-articular positions. In this case they were thought to be similar to rheumatic nodules. Their association with the chronic arthritides has long been recognized. Dawson and Boots' paper, published in 1930, contained a photograph of an arthritic patient with juxta-articular nodules, which were similar in all respects

to those seen in syphilitics. Furthermore, their description of the histological appearance of the lesions could hardly be differentiated from the description given by the Harvard Expedition (11) of the nodes in yaws, or from the description given by Jessner (12) and others of the nodes in syphilis. Dawson and Boots have obviously failed to appreciate the frequent rôle of syphilis in the causation of these nodules.

Attempts to establish histo-pathological or other criteria by which one may identify any individual nodule have been disappointing. Crouzon and Bertrand (13) noted a great similarity between the histological appearances of rheumatic and syphilitic nodules. In turn, Coates and Coombes (14) state that the nodes occurring in rheumatic fever, rheumatoid arthritis, Still's disease and subacute bacterial endocarditis are histologically identical. Jordan (15) described a case of juxta-articular nodules the histological picture of which suggested to him sarcoid. The excellent histological studies of the Harvard Expedition of nodes removed from patients with yaws add little to the subject. The expedition's workers did establish the fact, however, that such nodes may be occasionally due to filariasis, for they were able to aspirate filaria from the nodes in one such case. Furthermore, they noted the frequent presence of xanthoma, or foam cells, in the lesions, an observation previously reported by Jessner. Although Van Dijke and Oudendal (16) reported the finding of Treponema pertenue in the nodes of yaws, confirmation of this feature has been lacking. Clawson's (17) extensive review concerning the Aschoff nodule of rheumatic fever contains no reference to characteristic features found in the subcutaneous type. Swift (18), however, and more recently Rich (19), state that they may contain cell aggregates highly suggestive of Aschoff bodies. Until recently, animal inoculations of syphilitic nodes have been unsuccessful. Jessner and Rossiansky (20), however, recently secured a take in rabbits inoculated with material from a syphilitic juxta-articular node. Syphilitic lesions did not appear in the first animal, but lymph-node transfer, from this rabbit to another rabbit, produced characteristic lesions in the second animal.

In the Syphilis Clinic of the Johns Hopkins Hospital we have studied fourteen patients admitted with subcutaneous nodules of the juxta-

articular type. Twelve of them were females. Nine were negroes, five whites. The blood Wassermann was positive in thirteen. Eight of the patients had other clinical manifestations of syphilis. All but two of the patients had nodules characteristically placed over the extensor surfaces of the forearms near the elbows. In two cases they were unilateral in this location. Four had nodules also over one or both tibial tuberosities. In one patient, the nodes were generalized.

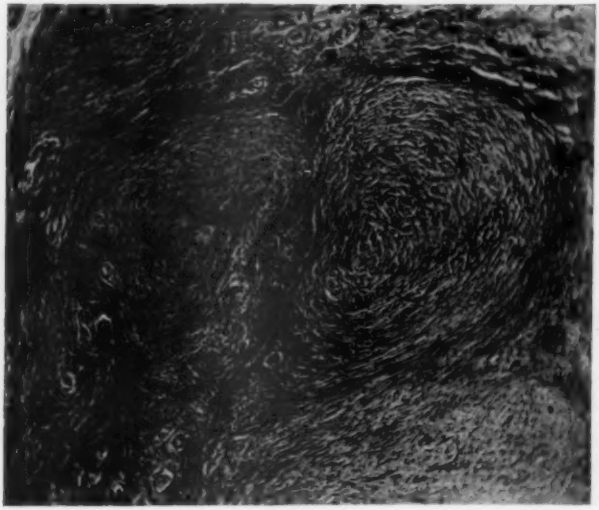

FIG. 1. CASE NO. UNIT 11891. SECTION TAKEN FROM A NODE EXCISED FROM A COLORED FEMALE OF 32. BLOOD WASSERMANN POSITIVE. NO OTHER EVIDENCE OF SYPHILIS
The remaining nodes disappeared rapidly under treatment with arsphenamine

Eight of the patients returned regularly for antisyphilitic treatment and in seven of them the nodules disappeared completely after one or more courses of six injections of arsphenamine plus interim bismuth. In one case the nodules persisted almost one year before they completely disappeared.

Nodes were excised from four of the patients and studied histologically. Staining by the Warthin-Starry method revealed no spirochaetes. Elastic tissue stains showed no elastic tissue except an

amount normally to be expected in the walls of the blood vessels. The nodes were made up mainly of whorls of fibrous tissue, infiltrated with epithelioid, plasma, round, and occasional giant cells. There was some tendency to perivascular infiltration, and areas of central vacuolization and necrosis were common. The picture did not differ essentially from that previously described. Zanthoma cells were present in nodes from two of the patients (see fig. 1). The picture could not be considered entirely characteristic of syphilis or of any other disease. Curiously enough, one of the nodes on section

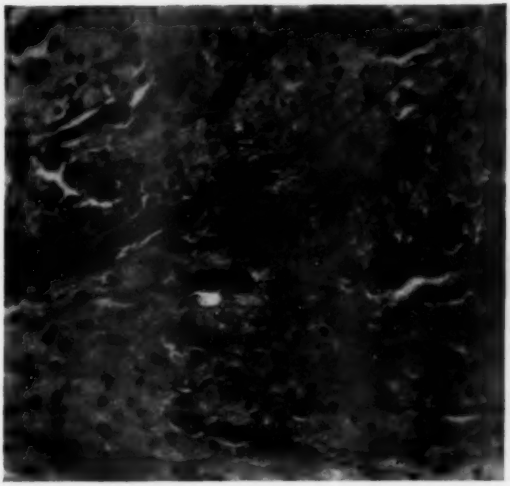

FIG. 2. CASE NO. J 52813. JUXTA-ARTICULAR NODULE, A PURE XANTHOMA

proved to be a pure xanthoma (see fig. 2). The patient from whom this node was taken gave a positive Wassermann, and the juxta-articular nodule that was not removed disappeared under treatment with arsphenamine. It was, however, much smaller than the one removed, and may well have been inflammatory, and not xanthomatous in character.

Material from a node excised from one of the patients (see figs. 3, 4), was inoculated by Dr. Turner into a rabbit's testicle. The animal remained normal. After three months lymph-node transfer proved

FIG. 3. CASE NO. J 54282. JUXTA-ARTICULAR NODULES IN A COLORED WOMAN OF 38, WITH SUBACUTE SYPHILITIC POLYARTHRITIS. BEFORE EXCISION AND TREATMENT

FIG. 4. CASE NO. J 54282. SIX WEEKS AFTER EXCISION AND TREATMENT. NODULES HEALED. HISTOLOGICAL PICTURE SIMILAR TO FIGURE 1

FIG. 5

FIG. 6

FIGS. 5 AND 6. CASE NO. J 46841. CHRONIC INFECTIOUS POLYARTHRITIS. NO EVIDENCE OF SYPHILIS

negative, the second animal being observed for three months. The histology of the inoculum node was similar to the others examined, and the remaining node disappeared after six injections of neo-arsphenamine. The nodes in this case were associated with a subacute syphilitic polyarthritis, which likewise cleared up rapidly under treatment.

FIG. 7. CASE NO. UNIT 34172. CHRONIC ARTHRITIS, SYPHILIS. GENERALIZED NODULES FAILING TO HEAL UNDER NEOARSPHENAMINE

Two of our patients were of exceptional interest. The first, J 46841, a white female of 41, had suffered from a chronic infectious polyarthritis for several years. There was no evidence of syphilis, and the blood Wassermann was negative. While under observation, the patient developed typical juxta-articular subcutaneous fibroid nodules in the usual location near the elbows (see figs. 5, 6). Because

of this silver arsphenamine was administered, and the nodes involuted to one half their original size after a few injections. Unfortunately, a biopsy from this patient was not obtained, and no explanation for the involution of the nodules is forthcoming. The second case, Unit 34172, exhibiting generalized nodules, has been referred to earlier in the text. This patient, a white insurance salesman of 40, was admitted with a moderately severe chronic infectious polyarthritis. There was

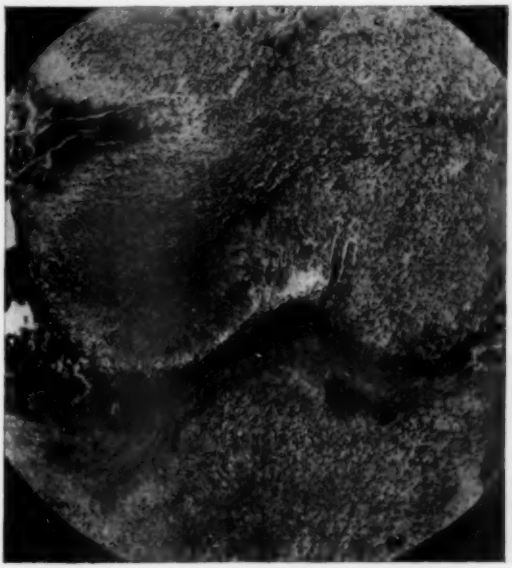

FIG. 8. CASE NO. UNIT 34172. SECTION OF NODE TAKEN FROM ELBOW SHOWING EDGE OF AREA OF CENTRAL NECROSIS

a history of chancre, and the blood Wassermann was positive. He presented a most remarkable picture of generalized subcutaneous fibroid nodules. They were visible and palpable over the occiput, auricles, back of the neck, near the elbows, over the fingers, sacrum, tibial tuberosities, and Achilles tendons (see fig. 7). Under neo-arsphenamine and potassium iodide the patient's general condition improved somewhat, but the nodules remained uninfluenced. A lymphatic gland from the groin was excised for study as well as one

subcutaneous nodule from over the tibial tuberosity, a second from the finger, and a third and fourth from a region near both elbows. The gland appeared normal. Sections of the nodules presented a remarkable picture, different but not strikingly so from the other nodules studied, and exhibiting features pointed out by students of both syphilitic nodules and rheumatic nodules as characteristic, respectively, of these two diseases. Xanthoma cells were present in the node from the finger (see fig. 8). In spite of this histological picture, which was not irreconcilable with syphilis, one had to conclude, on the basis of a negative therapeutic test, that the nodules were not syphilitic. In both of these patients we considered rheumatoid arthritis to be the exciting cause of the nodes.

DISCUSSION

Reasoning from evidence gleaned from the literature, and from our own experience, we believe that subcutaneous fibroid nodules, even of the juxta-articular type, are not pathognomonic of any single disease. It has been clearly shown that they may be associated with rheumatic fever, with the chronic rheumatoid arthritides, with yaws, possibly leprosy, syphilis, filariasis, scleroderma, acrodermatitis chronica atrophicans, and further, that they may be simulated by xanthomata. No doubt they will be reported as occurring in the course of other diseases. Histologic study is of small assistance in deciding the etiology of an individual node. Recourse must always be had to associated clinical signs and laboratory findings. In the case of suspected yaws or syphilis, the therapeutic test alone may decide the question. In this country the lesions are met with almost entirely in the rheumatic diseases and in syphilis. The juxta-articular areas have been a favorite location for the nodules in both of these diseases It is worthy of note, however, that in our experience the syphilitic juxta-articular nodules have never occurred in any other locations, whereas in arthritics they have always been more or less generalized.

SUMMARY AND CONCLUSIONS

1. Fourteen patients with subcutaneous nodules of the juxta-articular type are reported.

2. In twelve of the patients the nodes were syphilitic and in two they were associated with chronic infectious arthritis.

3. The syphilitic nodes healed completely under antisyphilitic treatment; the nodes associated with chronic infectious arthritis did not.

4. The histo-pathological picture of the nodes in syphilitics could not be considered conclusively characteristic of syphilis, nor could it be differentiated from the picture of the nodes associated with chronic infectious arthritis.

5. Spirochaetes could not be found in the syphilitic nodes, and one rabbit inoculation was negative.

6. Subcutaneous nodules of the juxta-articular type are not pathognomonic of any single disease.

7. Juxta-articular nodules may be simulated by xanthoma.

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PINOCYTOSIS

WARREN H. LEWIS[1]

From the Department of Embryology, Carnegie Institution of Washington, and The Johns Hopkins Medical School

Pinocytosis, drinking by cells; *phagocytosis*, eating by cells. The word "pinocytosis," suggested by my colleague Prof. David M. Robinson, is derived from the Greek πίνειν, to drink, and κύτος a cell. Certain cells in our tissue cultures, especially the macrophages, take in globules of fluid from the surrounding medium. This fluid part of the medium or serum of the blood-plasma clot, which is often liquefied, contains various proteins, globulins and other complex substances which supposedly do not diffuse into the cells. In addition, the fluid contains water and various salts. By pinocytosis the cells are able to take in substances which cannot diffuse into them or be taken in by ordinary phagocytosis of semisolid particles. The importance of this phenomenon in cellular metabolism and in the economy of intercellular fluids seems almost self-evident. The films (1) showing this phenomenon have been exhibited in various parts of the country during the past two years so that many are more or less familiar with the process. Dr. Manwaring's (2) editorial ("Hydrophagocytosis") from which the following quotation is taken indicates appreciation of its importance. "Physiologists will find in the Lewis phenomenon suggestion of a new mechanism of cellular nutrition and mechanical filtration or purification of body fluids. Immunologists will see in it confirmatory evidence of Metchnikoff's belief that the macrophages are the main place of disposal of soluble antigens, and the logical chief site of synthesis of specific antibodies."

The following observations are based for the most part on cultures of the omentum of the rat in auto- and homoplasma. These cultures give great numbers of migrating macrophages and monocytes and various transition forms between them. Many of the migrating

[1] Submitted for publication May 25, 1931.

macrophages become more or less flattened out on the coverglass as they move away from the explant. This is especially so in cultures where considerable liquefaction of the plasma clot has taken place about the explant. Motion pictures of these cells migrating on the coverglass revealed for the first time pinocytosis. Some one would no doubt have ultimately observed it by following cells in the ordinary manner, for, after we had seen it in the motion pictures, we were able to follow it under the microscope.

The wavy sheet-like processes or thin membranous pseudopodia of the macrophage series (3)—monocytes, macrophages (clasmatocytes), epithelioid cells—are often elaborate and project out from the body of the cell as waving sheets. The curious motions which they undergo are much emphasized by motion pictures (4). They tend to spread out widely on the coverglass when the cells are migrating on it, but they may also project downward into a fluid medium where there is no chance for attachment to a solid or semisolid support. They are best seen and followed in cells that are spread out on the coverglass (figs. 1 to 16).

The form and size of the macrophages vary greatly, and with these variations go variations in the size and extent of the membranous pseudopodia. Changes in form of the individual cells are continuously taking place along with continuous changes of the pseudopodia. When the macrophages are flattened out evenly on the coverglass, they have a circular or oval outline, and a wide membranous pseudopod spreads out from the entire periphery of the cell onto the coverglass. From this extreme condition there are all sorts of variations of semi-flattened cells, fan-shaped cells and multipolar cells to much elongated spindle-shapes with several small membranous pseudopodia at the tips, along the processes and on the body of the cell. The semi-flattened and fan-shaped ones are numerous. The cells readily change from one form to another. The semi-flattened cells have a broad pseudopod on one side and a convex thick edge on the other. The fan-shaped ones have a broad pseudopod on the wide end and smaller ones at the narrow end and frequently also on the body of the cell and along the sides of the narrow part. These smaller petal-like pseudopodia are very active throughout their whole extent and there is usually a rather abrupt transition from such a pseudopod to the body.

The large broad membranous pseudopodia which extend out onto the coverglass show a more gradual transition into the thin edge of the body of the cell, and there is often some doubt as to just how much to designate as pseudopod.

The peripheries of these broad wavy veil-like membranous pseudopodia form the most active part. The periphery is like a ruffle the free edge of which is much longer than the more proximal circumference, and consequently it is thrown into a series of folds, while the more proximal part of the thin pseudopod may be relatively flat. The width of the ruffle edge varies from time to time and its folds are continuously in motion. The flattened, more proximal part of the membrane tends to cling more firmly to the coverglass over its entire extent and shows, as a rule, much less change than its periphery. The ruffle edge, on the contrary, is attached only here and there to the coverglass, and these attachments are continuously changing as the membranes wave to and fro. Concerning the factors involved in producing this motion one can surmise that there are rapid changes in the physical states of adjoining areas accompanied by changes in surface tension.

The fluid globules which are taken up at the periphery of the wavy veil-like membranous pseudopodia seem to get caught or trapped in the folds of the ruffle, which probably then fuse around and completely enclose them. This process takes only a few seconds. The globules are at first irregular in outline but they soon become circular and probably spherical in form, presumably after they have become pinched off from the surface layer and lie free in the cytoplasm of the pseudopod but surrounded, however, by a thin surface film which was originally a part of the surface membrane of the cell. One cannot see exactly how the folds enclose and fuse about a globule of fluid, but there can be no doubt about the fact that globules do actually get into the cell and then move rapidly towards the center. It frequently happens that the peripheral folds seem to enclose a globule which, however, disappears after a few seconds. Such globules are probably only partially enclosed and the fluid escapes to the outside. The fact that the initial form of the globule is irregular is important as indicating that fluid is trapped by the irregular folds rather than that there is a rapid diffusion of fluid into the cell and accumulation there into droplets.

The initial size of the globules or vacuoles varies greatly in the same cell and in different cells, at different times and under different conditions. Sometimes most of them are large and few in number, or there may be large and small ones; or there may be only small ones and many may be going into the cell. At other times there is no visible pinocytosis. These differences probably depend upon the state of the metabolism of each cell, because cells side by side in the same culture show all sorts of variations of the above phenomenon. I have now nine different films of macrophages from cultures of the omentum of the rat. The cultures vary from one to seven days old and all of them show pinocytosis.

As soon as the globules or vacuoles of fluid become enclosed within the pseudopod, they move toward the center of the cell with gradually increasing speed and within one to five minutes reach the periphery of the zone of fat globules and granules which surround the central area and nucleus. The globules usually penetrate into the granular zone and then rapidly decrease in size so that in the course of a few minutes (1 to 5) they become reduced to granules which are lost among the other granules and fat globules. During the movement of the globules toward the center of the cell they frequently fuse with one another to form larger globules (figs. 1 to 16). This seems to be especially true where the initial size of the globule is small. Several globules are often taken in at approximately the same time in the same and in different regions of the periphery. The factors involved in propelling the vacuoles to the granular zone of the cell are unknown.

If neutral red is added to the culture medium the granules and vacuoles in the central part of the cell almost immediately take up the dye, but the new vacuoles at the periphery of the cell show no trace of it. During the few minutes occupied by the movement of such vacuoles toward the center of the cell, they gradually take up the dye and after they reach the granular zone continue to become darker until they are deep red in color. As the vacuole decreases in size, the red color becomes more pronounced and the residual granule which remains is very deeply stained with dye. Sometimes the vacuoles pass so rapidly toward the central part of the cell that they arrive there with very little color and when in that position gradually assume a deeper and deeper tint of the neutral red. The gradual acquisition

of the neutral red color in the vacuoles is indicative of some change going on within them, and it is not unreasonable to assume that some sort of a digestive fluid is being poured into them from the surrounding cytoplasm which rapidly digests the complex substances contained within.

The decrease in the size of the vacuole is probably due to two factors: (a) the excretion of fluid, probably mostly water and waste products, by diffusion into the surrounding medium, and (*b*) the digestion of the residual contents of the vacuole and the secretion of part of this, not utilized for the building up of the cell, into the surrounding medium. There were no indications that the contents of the vacuoles suddenly escaped to the outside by breaking through. Occasionally these globules or vacuoles persist for a relatively long time, an hour or more.

The amount of fluid taken into these cells under certain conditions is relatively enormous, for sometimes one vacuole after another, and often several at a time, can be seen passing from the periphery to the central part of the cell. The total volume of such vacuoles may in the course of an hour amount to one-third the volume of the cell. For example, cell no. 1, film 37, took in 80 globules during the course of an hour. Of these 32 were from 1 to 2.5 micra and 48 from 2.5 to 5 micra in diameter. A rough calculation of the total volume of the 80 vacuoles was in the neighborhood of 1500 cu. micra and that of the cell about 4500 cu. micra. Cell no. 15 took in 56 globules from 1 to 6 micra in diameter in the course of an hour. Cell no. 13 took in 140 globules in one hour and forty minutes varying from 1 to 5 micra in size. Sometimes there were as many as ten vacuoles at one time, mostly small ones, and sometimes there were intervals of 4 to 6 minutes when no entering globules were noted. Cell no. 35 took in 60 globules from 1 to 6 micra in diameter in thirty minutes. Here there was a tendency for the small globules to enter in groups and for the larger ones to be few in number (1 to 4).

We have no adequate means of measuring the amount of fluid which passes in and out of an active cell by the usual process of diffusion, but the rapidity with which neutral red diffuses into a cell and is caught there by certain granules and vacuoles indicates that by diffusion large volumes of fluid pass in and out of cells without materially

increasing or decreasing permanently the total volume of the cell itself. The observations on pinocytosis enable us to estimate in a rough way the amount of fluid taken up as globules and excreted or secreted by these cells. This probably amounts to several times the volume of a cell in twenty-four hours.

This phenomenon has not been folowed in cells as they exist under normal conditions in the body, but there is no reason to suppose that the process does not go on there perhaps to an even greater extent than in cultures, for cells which have been examined in fresh spreads of the deep fascia show that the macrophages are more abundantly supplied with these wavy film-like pseudopodia than they are in the cultures. These cells also contain numerous fluid globules or vacuoles of various sizes.

Pinocytosis is not peculiar to the macrophage series, for some of my films show active pinocytosis by sarcoma cells from both the rat and the mouse and also by carcinoma cells from the rat. Normal fibroblasts from the omentum of the rat also exhibit it. Pinocytosis may be a much more universal process than we at present suspect. One wonders if the endodermal epithelium of the alimentary canal exhibits this phenomenon, for if so it would help to explain the rapid taking up of certain products of digestion.

The crucial point of the phenomenon of pinocytosis concerns the initial formation of the globules. Are they actually entrapped *in toto* from the surrounding fluid, or do they arise by the progressive fusion or enlargement of initial small ultramicroscopic globules of fluid which has diffused into the periphery of the cell? Fluid undoubtedly diffuses into and out of cells but whether such fluid forms vacuoles or not is another question. Vacuoles undoubtedly accumulate in degenerating cells in large numbers and they increase in size from just visible ones to large ones without much fusion and without any especial increase in cell size. Such degeneration vacuoles develop about the central region of the cell rather than at the periphery and are probably due to autodigestion and accumulation of the resulting waste products without any special diffusion into the cell. The peripheral entrapped fluid globules due to pinocytosis by apparently normal cells often start out suddenly as fairly large bodies with no evidence of having progressively increased in size at the periphery (see

globules at (*e*) and at (*f*), plates I and II). Such globules may pass to the center and disappear without any special increase in size. They could not be produced in any other manner than by the sudden entrapping of fluid in the folds of the wavy pseudopodia. The sudden entrapping of smaller but clearly visible globules at the periphery and their subsequent fusion into larger and larger ones as they pass towards the center is more usual than the sudden entrapping of the large ones.

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PLATE I

FIGS. 1–16. Pinocytosis and changes in form of a large film-like pseudopod of a fan-shaped macrophage, from a twenty-four-hour culture of the omentum of the rat, × 660 diameters. The photographs are at one-minute intervals. The film was made at the rate of 5.3 frames per minute and at an initial magnification of 165 diameters. The two globules (*a*) figure 1, are fused in figure 2, much reduced in size and within the granular zone in figures 3 and 4, and have practically disappeared in figure 7. Globule (*b*) passes to granular zone in figures 1, 2 and 3, becomes reduced in size in figures 4, 5 and 6 and is gone in figure 7. Small globules trapped in a specially wavy region at (*c*) figures 2 and 3, fuse to form larger globules in figure 4, which in turn fuse into a large globule. It and small globules move toward granular zone (figs. 6, 7 and 8), penetrate in among the granules and decrease in size (figs. 9, 10 and 11) and are lost in figure 13. Globules (*d*) entrapped at edge of pseudopod (fig. 12) moves toward the center (figs. 13 and 14) and fuse in granular zone (fig. 15). Globule (*e*) entrapped at edge of pseudopod, (fig. 9), moves toward granular zone (fig. 10) and is reduced in size (fig. 11). Globule (*f*) entrapped at periphery (fig. 12), moves to granular zone (figs. 13, 14 and 15) and decreases in size (fig. 16).

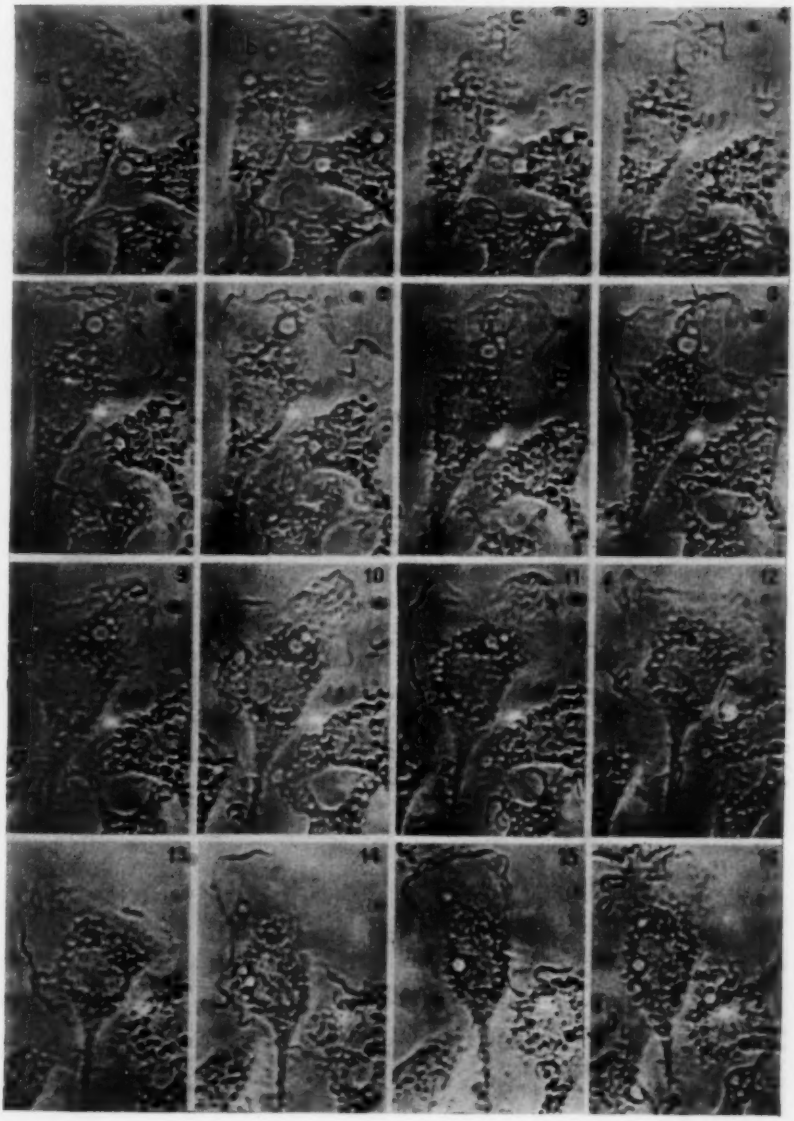

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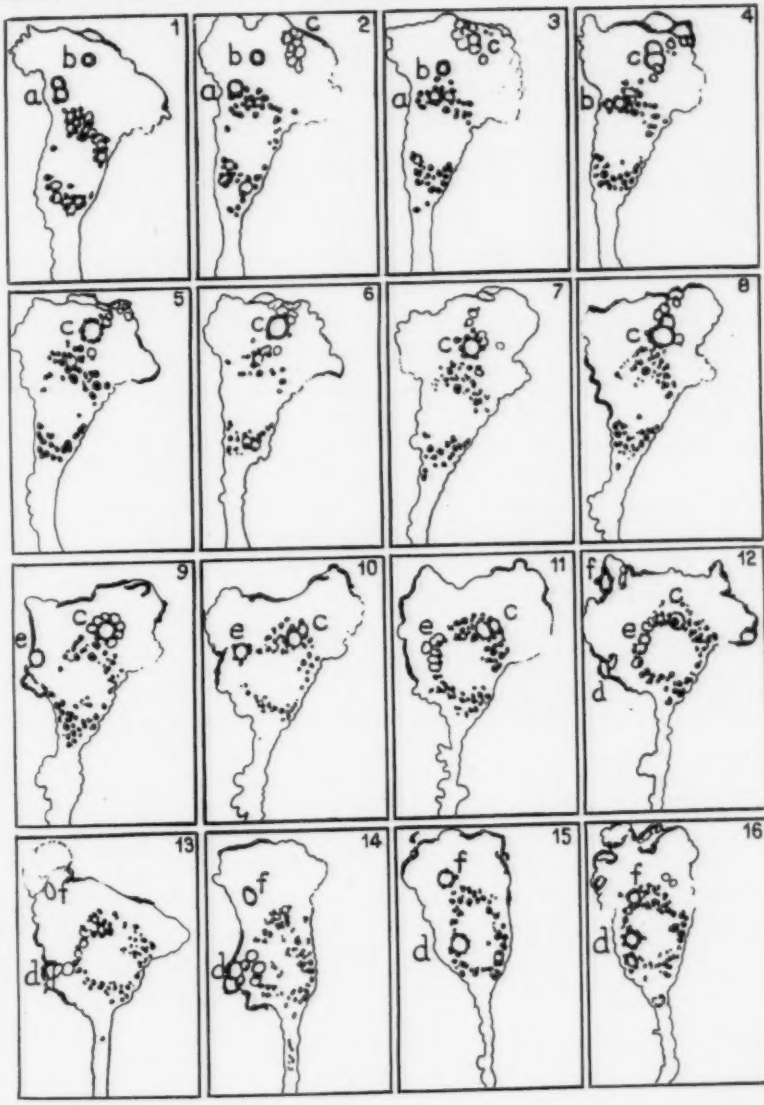
PLATE II

FIGS. 1–16. Diagram cell 1, plate I. In places the outline of the large pseudopod is too thin and delicate to be determined exactly.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LOCOMOTION OF LYMPHOCYTES

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The study of our motion pictures indicates that the mode of migration of lymphocytes is essentially similar to that of the amoeba as described by Mast.[1] Lymphocytes are so small that not all the processes and the structures observable in the amoeba can be seen in them, but enough can be made out to show the similarity. The essential features of locomotion in these two types of cells are (1) local softening or solation with (2) the formation of a pseudopod due to (3) the contraction of an outer plasmagel layer which forces (4) the inner plasmasol forward, while (5) the plasmagel remains fixed as regards objects in space except at the (6) posterior end of the cell where its inner surface is continuously being transformed into the plasmasol which (7) after being forced forward by the contraction of the plasmagel is continuously changed again into the plasmagel state at the continuously advancing anterior rim of the plasmagel tube.

Motion pictures, of migrating lymphocytes from cultures of lymph nodes of rats in auto- and homoplasma, were taken at the rate of 24 frames per minute or one every $2\frac{1}{2}$ seconds. When projected at the normal rate of 16 frames per second the movements of the lymphocytes are speeded up 40 times. This is much too fast to get more than a general impression of their behavior, such as periods of rest and activity, alteration in direction, changes in form and persistence of anterior and posterior ends during a migration period. The

[1] Mast, S. O., 1926. Structure, movement, locomotion and stimulation in amoeba. *Jour. Morph. and Physiol.*, vol. 41, pp. 347–425.

Lewis, W. H., 1931. On the locomotion of lymphocytes. *Anat. Rec.*, vol. 48, Supl., p. 52.

detailed studies of individual lymphocytes were made by projecting one frame after another and making drawings or photographs of individual lymphocytes as they appeared in successive frames. In this manner one can determine the paths of migration, the rate of migration and changes in form at 2½ second intervals or any multiple thereof. Since the frames can be projected so that each enlarged image is exactly superimposed on the place occupied by the previous one, the above changes can be determined with mathematical exactness, provided the photographs are sharp and distinct, which is rarely the case with these cells because of the extreme delicateness of the pseudopodia and changes in focus. The following observations are based for the most part on film No. 96 from a 24-hour culture kept at a temperature of 38.5° to 38.9°C. and filmed for 49 minutes, at a magnification of 165 diameters. The enlarged projected images were for the most part 2000 diameters.

During a period of rest the lymphocyte is spherical but pseudopodia are sometimes thrust out and retracted without producing more than a slight wabbling motion of the whole cell. When, however, the rest period is over and the lymphocyte begins to migrate, a single pseudopodium flows out from a relatively small area. As the pseudopodium enlarges, a groove develops at its base where it joins the body of the cell. This groove or constriction ring corresponds to the rim about the softened area which gives rise to the pseudopod. As the pseudopod increases in length and breadth the groove usually becomes more marked. Thus when the groove first appears, in front of it is the expanding pseudopod and behind it the body of the lymphocyte with its large nucleus.

The cytoplasm at the bottom of the groove and on the surface of the body seems to be denser than that in the pseudopod and is probably in the gel state, while that of the advancing pseudopod is fluid and in the sol state except for a very thin surface layer. As the pseudopod extends farther and farther forward, there are progressive changes in the region in front of the ring as though there were an anteriorly progressive gelation of the superficial part of the cytoplasm which then comes to resemble that of the body. The significance of this will be discussed later.

The interesting thing about the groove is that it does not move

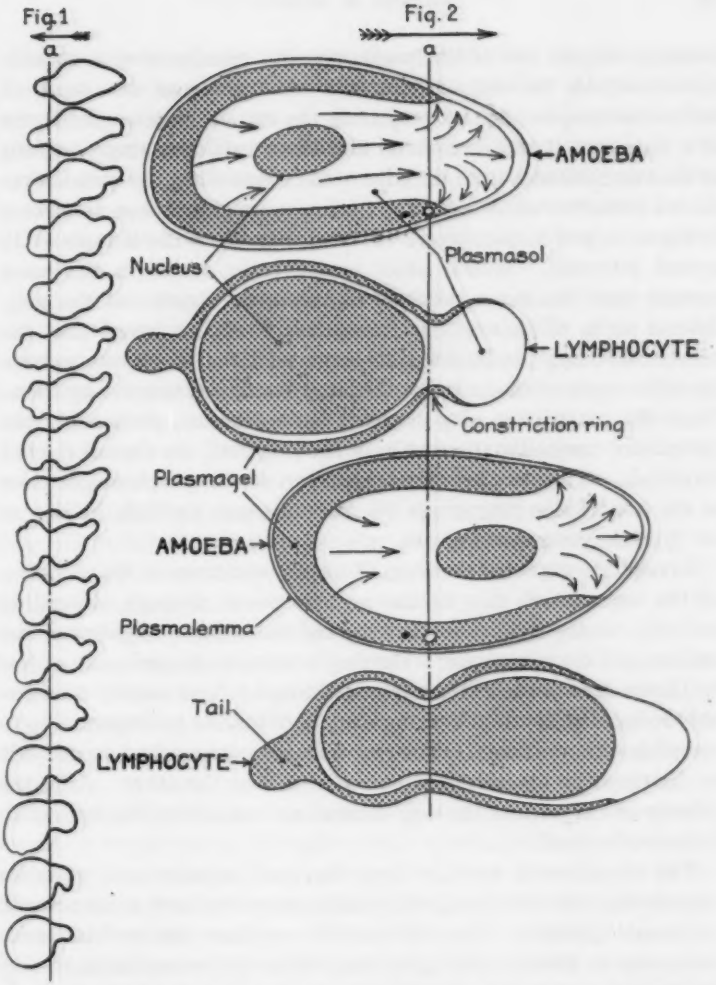

FIG. 1. CHANGES IN FORM OF LYMPHOCYTE NO. 1 AT 2½-SECOND INTERVALS SHOWING THE FORWARD MOVEMENT OF THE CELL WHILE THE CONSTRICTION RING REMAINS FIXED AS REGARDS THE OBJECT (*a*) OUTSIDE THE CELL

The line from (*a*) is at a constant distance from the edge of the frame. The drawings were made by projecting successive frames.

FIG. 2. DIAGRAM COMPARING LOCOMOTION OF AMOEBA AND OF A LYMPHOCYTE

forward with the rest of the lymphocyte but remains fixed as regards objects outside the cell. It was only when drawings were made of individual lymphocytes by projecting the motion pictures one frame at a time that it was discovered that the constriction ring remained at the same distance from the edge of the frame while the lymphocyte moved toward or away from it. Such a series of drawings are shown in Figure 1, and as each frame was used, they show the changes at 2½ second intervals. Several other lymphocytes drawn in the same manner show the same relations regarding the fixation of the ring. Several series of photographs from other films also reveal that the constriction rings maintained constant relations to objects outside the cell in spite of the fact that the latter continued to move by them. Since the constriction ring does not move forward, presumably the cytoplasm, composing it, remains in the ring until the time of the tail formation. Thus, not only the nucleus but all the cytoplasm posterior to the constriction ring except the tail must pass through the ring as the lymphocyte moves forward.

As might be expected there are all sorts of variations in the condition of the constriction ring as the nucleus passes through, depending probably on the rigidity of the ring and the relative turgidity of the nucleus and the cytoplasm. The ring is always enlarged more or less by the nucleus as the latter is forced through it, and usually considerably reduced in depth. Varying degrees of this are encountered up to complete disappearance. The ring may be more marked on one side or disappear on one side and partly remain on the other. After the passage of the nucleus the ring contracts down behind the nucleus to form a nub or tail.

The lymphocytes tend to keep the same anterior and posterior ends during a period of migration which may vary from a few seconds to several minutes. The tail is a very constant feature but varies from time to time according to the position of the constriction ring. It is most prominent after the ring contracts behind the nucleus. It may shorten or almost disappear between the constriction rings, but there is usually some indication of it during the entire migration period.

It takes from 20 to 50 seconds for the body of the lymphocyte to pass through a constriction ring in the cells thus far examined at 38° to 39°C.

As the nucleus passes through the constriction ring it becomes elongated and the whole cell also becomes elongated at the same time. After the nucleus has passed through the ring, it becomes more spherical again and the lymphocyte shortens. When there is a succession of rings the lymphocytes undergo a corresponding succession of elongations and shortenings, unless the rings follow one another at relatively short intervals in which case the lymphocyte remains more or less elongated.

Most of the lymphocytes have a succession of rings during a migration period which form at irregular intervals. This gives to the lymphocyte an intermittent sort of progression. Lymphocyte no. 3, for example, during a part of a migration period, had five constriction rings, two of which were always present at the same time. Some of them became very indistinct or disappeared until they contracted down to form the tail. Number 1 ring lasted from 0 to 35, No. 2 from 25 to 50, No. 3 from 40 to 60, No. 4 from $52\frac{1}{2}$ to $77\frac{1}{2}$, and No. 5 from $67\frac{1}{2}$ to $92\frac{1}{2}$ seconds after the start of the observation at 0.

The depth of successive rings or grooves may vary considerably on the same lymphocyte, indicating variations in the strength of the contraction of the ring or variations in the turgidity of the nucleus or both in relatively short intervals of half a minute more or less. The fact that the groove may entirely disappear does not mean that the ring has ceased to exist, for it seems to become evident again after the nucleus has passed through it by contracting down to emphasize the tail.

The lymphocyte squeezes through the ring much as one would imagine it would squeeze through a small opening between endothelial cells. In our migrating lymphocytes the groove is not produced by an external factor, for they migrate in this way when they are on the coverglass in a fluid medium. When they are in a thick plasma clot they do sometimes squeeze through small meshes of the fibrin and it may be that since lymphocytes have been so accustomed, for thousands of generations, to squeezing through tight places they go on acting this way even when there are no small holes to go through. In other words, this groove formation is an inherited feature.

My observations indicate that lymphocytes are attached more strongly to solid or semisolid supports on which they migrate, by

the anterior end or pseudopod than by the body. Both the body and the tail often swing rather suddenly to one side or the other as the lymphocyte changes direction as though the body was not attached at all. When the lymphocytes round up on the under surface of the coverglass in a fluid medium, they frequently lose their attachment and fall to the bottom of the drop, where they may collect in large numbers and there migrate about on the surface film of the fluid.

Mast's observations and discussions on the locomotion of Amoeba proteus are of special value for the understanding of the locomotion of the lymphocytes. Such facts as we have been able to ascertain regarding these minute cells fit in so beautifully with those observed by Mast on the relatively huge amoeba that one must conclude that the mode of locomotion of the amoeba and that of the lymphocyte are essentially similar. The most important fact in this regard is the fixity of the constriction ring as regards objects in space. This corresponds to the similar fixity of vacuoles and granules in the plasmagel of the amoeba. We may well briefly review here Mast's conclusions regarding the locomotion of Amoeba proteus which are based on many observed facts.

The amoeba has an outer relatively thick semisolid layer, the plasmagel, and an inner fluid part, the plasmasol. The thin superficial plasmalemma of the amoeba has no recognizable counterpart in the lymphocyte (Fig. 2). In a state of rest the diffusion or osmotic pressure and the elastic tension of the plasmagel are in a state of equilibrium. When the amoeba is about to move, the plasmagel, adjoining the plasmasol, locally liquefies or solates, resulting in local decrease in thickness and in elastic strength. "This in turn, owing to the elasticity of the plasmagel and the turgidity of the amoeba, results in the stretching and bulging of the plasmagel in the region where it has become weakened and in the movement of the plasmasol toward this region. The bulge or protuberance thus formed is the beginning of a pseudopod." The thin plasmagel of the pseudopod, especially at the tip, owing to continuous contraction elsewhere and the resultant pressure of the plasmasol against it, is continuously stretched until it becomes a very thin sheet. There is a continuous rapidly streaming forward of the plasmasol in relation to points in space, while the thick plasmagel is everywhere practically at rest

The plasmasol gelates all along the edge of the base of the pseudopod, building the plasmagel tube forward as rapidly as the pseudopod extends. The plasmagel at the inner surface of the posterior end of the body solates as rapidly as it gelates at the anterior end.

Locomotion is doubtless due largely if not entirely to contraction in the plasmagel, especially or largely at the posterior end. It seems that contraction must be in some way associated with solation.

"If a granule or crystal in the central part of the streaming plasmasol is selected and pursued in its course, the following will be observed: It goes straight forward, either until it reaches or nearly reaches the inner surface of the plasmagel at the tip of the advancing pseudopod, then it deflects to the right or left, upward or downward, and sooner or later, directly or indirectly, comes into contact with the plasmagel at the base of the pseudopod, where it comes to rest and is, together with the medium in which it is suspended, transformed into plasmagel." Here it remains stationary in reference to points in space but not as regards the anterior and posterior ends of the amoeba which continue to move forward until finally the posterior end of the amoeba reaches the granule. The granule then moves inward and enters the plasmasol to repeat the whole process again. "There is in amoeba during locomotion a continuous transformation of the more solid substance into the more liquid substance at the posterior end and the opposite at the anterior end."

In arriving at an explanation of lymphocyte locomotion we shall need to make some assumptions. In the first place it can be safely assumed that the lymphocyte at rest is undergoing metabolism and that differential local changes result in a softening at one spot, and that the cytoplasm here becomes more fluid and the surface tension decreased. Any tension or contraction of the rest of the cell would result in the flowing out of a pseudopod. There are no indications that the environment produces any differential effects which result in the local solation, for in any given field lymphocytes are moving in various directions and even come into contact with one another and move by in opposite directions while other lymphocytes in the neighborhood are at rest. In the second place we can assume that the body of the lymphocyte must contract, otherwise the pseudopod would not be forced out from the local softened area. The third assumption

concerns the question of an outer plasmagel layer and an inner fluid part, the plasmasol, in which the nucleus lies. The fact that the pseudopod is localized indicates that the cytoplasm on the surface of the body must be more rigid than that of the pseudopod. There is also a corresponding difference in the appearance of the two regions. Concerning the thickness of the plasmagel and the amount of plasmasol we have no adequate data. The tail appears to be quite rigid.

With these assumptions and the facts at hand as already given, the similarity of the mode of migration of the lymphocyte and the amoeba is evident (Fig. 2). There is a local solation, and a pseudopod is thrust out by the contraction of the body of the cell. Contraction is probably not limited to the posterior region of the body of the lymphocytes, as Mast supposes it to be in the amoeba, because in the lymphocyte the contraction of the constriction ring and the distortion (elongation) of the nucleus indicate that contraction takes place over all the lymphocyte except the advancing fluid pseudopod. The assumption of a plasmagel layer and a plasmasol center and the continuous solution of the former at the posterior end with the continuous flowing forward of the plasmasol and the continuous gelation to form a continuously advancing rim of plasmagel is not unreasonable.

OBLITERATIVE PULMONARY ARTERIOLOSCLEROSIS

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Because it was to us an unfamiliar condition, and the only instance of the kind in about twelve thousand autopsies, the following case may be reported. It is by no means a new or inadequately described disease, however, for single cases have been studied in many parts of the world and about forty or forty-five have been published in detail. It is essentially an affection of the branches of the pulmonary arteries in which a very great thickening of the intima reduces the lumen to an extremely minute canal, or completely obliterates it.

The resulting symptoms are identical in all cases, the anatomical changes throughout the body are identical, but there remains complete obscurity as to the cause. Several suggestions have been made, most prominent being perhaps that originating with workers in Buenos Aires, that the change in the pulmonary arteries is due to syphilis. This would be a very satisfying explanation, and it is, of course, difficult to disprove it. On the other hand, many of the relatively young persons who die of this disease have had no history of syphilitic infection, the Wassermann reaction is negative and there are no other signs of syphilis. Spirochaetes have been found once but, as De Jong properly points out, there are many kinds of spirochaetes to be found in the lung. Further, the descriptions of unmistakable syphilis involving the pulmonary artery and its branches (Wagner and Quiatkowski, Peck and others) present lesions which have nothing in common with those found in the arteries in these cases. Others have found the pulmonary veins narrowed at or near their entrance into the heart, and have tried to show that this might cause an increased blood pressure in the pulmonary circulation just as in the case of mitral stenosis. They seem to ignore the fact that this must result in distension of the veins within the lung, and in the pigmentation and

other changes characteristic of chronic passive congestion of the lungs, none of which are found. The most extreme mitral stenosis fails to produce any such thickening and narrowing of the arterioles as is found in this disease, although the larger branches show plaques of sclerosis.

Still others regard the process as merely a special localization of arteriosclerosis even though the aorta and systemic arteries are always delicate and normal.

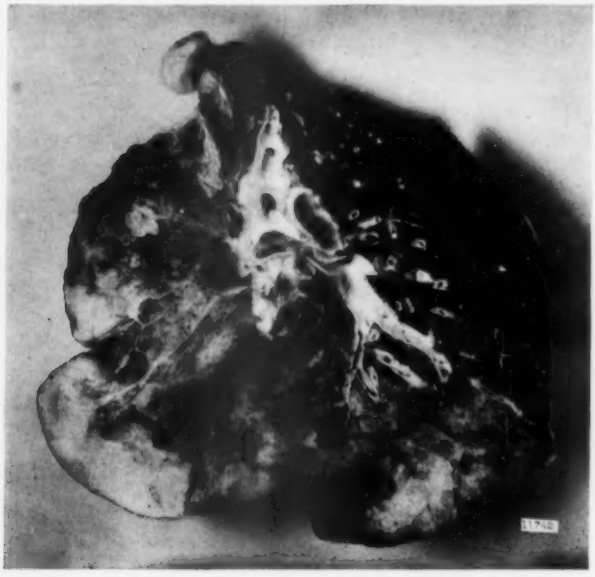

FIG. 1. RIGHT LUNG SHOWING THICKENED ARTERIES, INFARCT, ETC.

Another tentative suggestion related to this would refer the obstruction to a possible repeated contraction of the arterioles in successive anaphylactic shocks in a sensitized person. This could act on the arterial walls just as the heightened pressure following mitral stenosis is supposed to act. But, if human beings react in this way, the contraction would be temporary and occasional. Arrilaga, who afterwards became confident of the syphilitic origin of the change, at

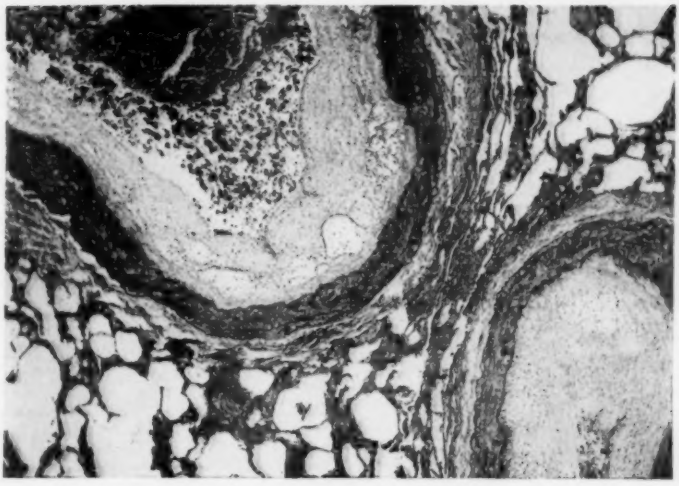

FIG. 2. SCLEROTIC PATCHES IN PULMONARY ARTERIES OF ABOUT 2 MM. DIAMETER

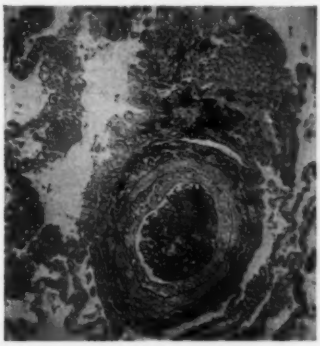

FIG. 3

FIGS. 3, 4, 5, 6, 7 AND 8. VARIOUS STAGES IN THE GRADUAL OBLITERATION OF ARTERIOLES BY THE SCLEROTIC PROCESS

first thought it occurred in those sensitized by some other disease such as syphilis or malaria, or some intoxication.

Typical cases of the sort have been described by Romberg, Mönckeberg, Bristowe, Mobitz, Mattirolo, Kidd, and many others, and ref-

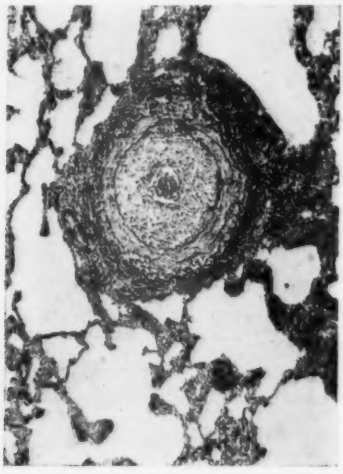

FIG. 4

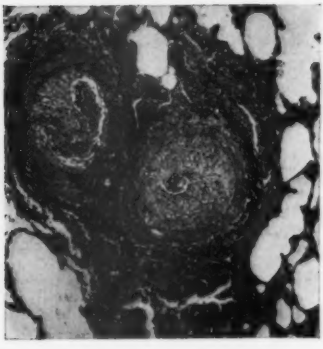

FIG. 5

erences to their papers are given. None of them, however, have any very convincing ideas to offer as to the aetiology. Cases in which repeated embolism or thrombosis has resulted in occlusion and re-

canalization of many of the small vessels, have been described by Goedel, Lang, Löwenstein, Ljungdahl and Moeller, but it seems obvious that these form a different class. Cases of unmistakable syphilis involving aorta and the main pulmonary arteries, with somewhat sim-

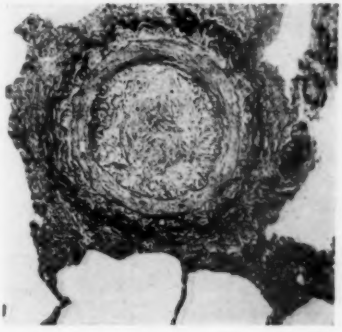

FIG. 6

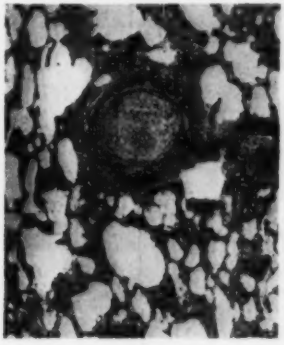

FIG. 7

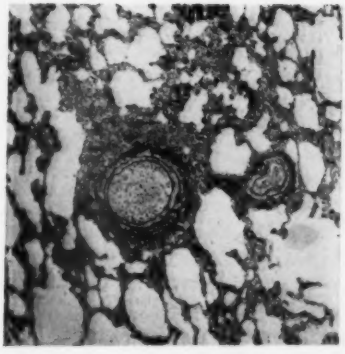

FIG. 8

ilar occlusion of the arterioles in the lung, are described by Wail, Plenge, Cheney, Sergent and Durand, Wagner and Quiatkowski, Peck, Warthin, Darre and Albot, De Jong and others.

The case recently observed was as follows:

L. J. A negro housewife, aged 39, was admitted to the hospital on November 11th and died December 5th, 1930.

She complained of pain in the stomach and shortness of breath. The family history was negative. At the age of 17 she had for a short time fleeting pains in various joints and frequent attacks of tonsillitis until she was 30, when they ceased. She bore two children at the ages of 22 and 27.

At 24 she began to be breathless on exertion. One year later she began to have fainting attacks, always associated with undue physical exertion and preceded by a sensation of fulness in the epigrastrium and tightness about the heart, but no pain. She could avert an attack if she heeded these symptoms and lay down, but if she continued her exertion, she would lose consciousness for some minutes and be left weak and nervous for several days afterward. In November, 1929, she underwent an operation in this hospital for the removal of a uterine myoma. The heart seemed perfectly normal at that time except for a systolic murmur to the left of the sternum and an accentuation of the pulmonary second sound. Convalescence was uneventful.

Four months before her second entry into the hospital the old symptoms returned with increased severity; cough, breathlessness, fulness of the abdomen and tightness about the heart confined her to bed. When she appeared in the hospital her temperature was 100°, pulse 125, respiration 24, blood-pressure 125/95; there was dyspnoea, moderate cyanosis and an occasional dry cough. She was extremely listless; the veins of the neck were engorged and pulsating. Except for a few fine râles at the bases both lungs seemed normal. The cardiac impulse was not particularly forceful. Dulness extended 15 cm. to the left in the sixth interspace, 4.5 cm. to the right in the fourth interspace. The heart sounds were everywhere loud. At the apex there was a marked presystolic gallop, a loud tympanitic bell-like first sound, a soft, low-pitched systolic murmur, and a faint mid-diastolic murmur. The pulmonary valve closure was easily palpable and produced a shock and conspicuously accentuated pulmonary second sound. The cardiac rhythm was regular. The liver produced a large, dome-shaped, swelling in the epigastrium. There was but little oedema of the extremities.

There was no anaemia and the leucocyte count was normal. The urine was concentrated and showed constantly 5 to 6 grams of albumin per litre, with occasional casts, leucocytes and red corpuscles in the sediment. The Wassermann test was negative. The electrocardiogram showed normal mechanism with a pronounced dextrogram. Later examinations of the blood, from November 11th to December 3rd, showed haemoglobin varying from 95–104–76 per cent; red corpuscles 5,000,000–6,270,000–4,600,000, so that polycythaemia was at least never marked. The pulse at the wrist was almost imperceptible, and during the week before death averaged 130 to 150. There was no fever nor any leucocytosis. A venesection afforded only temporary relief. She soon complained of cramp-like pains under the heart and frequently cried out with the pain. Finally, with nausea, dyspnoea, great restlessness, disorientation, delirium, pain in the chest and epigastrium, she lost consciousness and died.

FIG. 9. ORGANISING THROMBUS IN NARROWED ARTERY

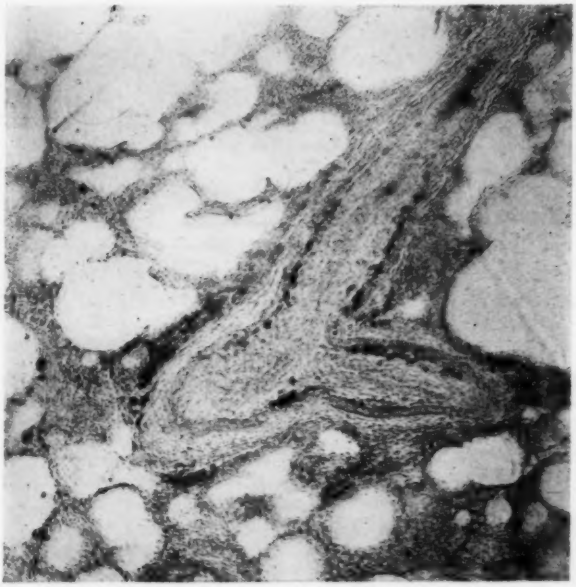

FIG. 10. FROZEN SECTION WITH FAT STAIN TO SHOW THE FAT IN THE DEEPER LAYERS OF THE THICKENED INTIMA

There is also coal pigment in the adventitia

The autopsy (11742) performed four hours after death may be recorded in brief.

The body is that of a well built negro woman about 165 cm. long. There is some oedema of feet, ankles, arms and thighs. There is extreme retraction of the gums with a purulent exudate about the teeth. Three of the upper incisors have been extracted and there is a deep depression above the root of one where an abscess existed. There is a median scar just above tne symphysis pubis, about 10 cm. long. The peritoneal cavity contains no excess of fluid; the surfaces are smooth and glistening. The organs are normally disposed except in the pelvis where the uterus, right tube and ovary have been removed. The pleural cavities contain no excess of fluid. The surfaces are smooth. The pericardial cavity contains about 40 cc. of clear fluid. The surfaces are smooth.

The heart is greatly enlarged, its apex far out to the left. The right auricular appendage is particularly prominent; the right auricle is enormously distended and practically forms the whole anterior surface. The right ventricle is also distended and is larger than the left. All the veins on the surface of the heart and the venous sinuses and inferior vena cava are greatly distended.

On cutting through the vena cava, the liver, which is deep purple and bulging so that an impression made with the finger is paler than the surrounding tissue, quite visibly collapses. On opening the heart the right side is found enormously distended with fresh clots. The tricuspid and pulmonary valves are normal. The wall of the ventricle is markedly thickened and firm—it measures 8 mm. in thickness, whereas the wall of the left ventricle measures only 12 mm. The left auricle is not distended but contains some clots. The mitral and aortic valves are normal. The foramen ovale is closed and so also is the ductus arteriosus. The coronary arteries are perfectly permeable throughout all their branches and their walls are smooth and of normal thickness. Their orifices are quite normal and the lining of the aorta is smooth throughout. The aortic orifice measures 6.25 cm. in circumference, while that of the pulmonary measures 8 cm. and the artery itself maintains this width. The heart weighs 390 grams.

The left lung is smooth superficially, pale and air-containing throughout. The bronchi seem normal. The only striking feature is the great widening of the pulmonary arteries which stand out as thick-walled tubes throughout the lung. Their walls are irregularly dilated and show patches of arteriosclerosis throughout, even in the smaller branches. The right lung may be described in practically the same words except that there is an emphysematous bleb about 2 cm. in diameter at the apex. The anterior portions of this lung seem slightly rarefied, but there is no marked emphysema. The arteries in this lung seem even more dilated and thickened than those in the left, and this condition extends even into the smaller branches. In the margin of the lower lobe of the right lung anteriorly there is a hard red triangular haemorrhagic infarction and the branch of the artery passing to this area is occluded by a dense mass of thrombus material. There is nowhere any pneumonic consolidation or any scarring of the lung tissue.

The abdominal organs present an advanced degree of chronic passive congestion

as illustrated by the liver but otherwise no gross changes are found. The abdominal aorta and its branches show no arteriosclerotic changes nor do the cerebral arteries. The brain shows no macroscopic alterations.

The *anatomical diagnosis* is as follows: Arteriosclerosis and arteriolosclerosis of pulmonary arteries with secondary thrombosis and organization of thrombi. Haemorrhagic infarction of right lung. Hypertrophy and dilatation of right auricle and ventricle. Extreme chronic passive congestion of viscera.

The microscopic study of the tissues other than those of the lungs and the arterial system presents nothing of special interest. There is evidence throughout the systemic circulation of advanced chronic passive congestion. There is nowhere any microscopical alteration of the tissues which could be interpreted as of syphilitic origin and this confirms the conclusions drawn from the study of the gross appearances. The aorta and all the smaller arteries appear quite normal. Especial attention was directed to the coronary arteries of the heart, the cerebral arteries and those of the abdominal organs, and in all cases normal conditions were found.

There remain the changes in the pulmonary artery and its branches. The larger branches show, as described, elevated plaques in the intima which in section are sometimes found to consist of a compact new tissue made up of elongated cells with oval nuclei. In most of the sections, however, it is found that the tissue which produces the great thickening of the intima is a very loose network with wide spaces filled loosely with large cells whose cytoplasm is finely vacuolated and evidently loaded with fat. There are spaces without such cells which contain free fat globules. The supporting tissue, when not so spread into a network, is made up of elongated cells as described. This is true of the smaller branches, 2 to 3 mm. in diameter, in which the thick intimal layer occupies a relatively larger part of the lumen, and in these the blood is often evidently stagnant and much disintegrated. Fat stains show a thick layer of fat globules in the lower strata of the intimal tissue. The media and adventitia appear quite normal—there is no disturbance of muscle or elastica and no perivascular wandering cell infiltration which could be suggestive of syphilis.

In the still smaller branches of the arteries—those arterioles which measure much less than 1 mm. in diameter—the building up of a new tissue in the intima with fat globules in its lower layers is seen in every stage, from a slight thickening of the intimal layer to a complete and solid occlusion of the lumen with the disappearance of the endothelial lining cells. In the intermediate stages when the narrowed and generally eccentrically displaced lumen is still evident, the endothelial cells are crowded together and thrown into folds. Frequently the blood in the lumen is plainly stagnant and the corpuscles partly disintegrated. Oftener still, there is a homogeneous or hyaline thrombus mass which is becoming recanalized by new-formed capillaries, and sometimes these can be seen in the thick intimal layer which causes the obstruction. It seems that the most rational interpretation of this situation, which is forced upon us indeed by the study of the

successive stages in its production, is that the new tissue is formed with its enclosed lipoidal material—the blood stream is obstructed and within and distal to the narrowed part it becomes a clot which undergoes organization. Indeed, in longitudinal sections of the arterioles the whole succession of events can be made out. In only one place has this been extensive enough to cause an infarction and that probably with the aid of the obstruction of neighboring arterioles.

There is, indeed, surprisingly little alteration in the lung tissue in general. The few pigmented cells which give an iron reaction certainly do not indicate a chronic passive congestion of the lung but have rather become pigmented from some of the neighboring organising thrombi. The idea that all this sclerosis of the arteries might be due to obstruction of the pulmonary veins at any point receives no support because the veins and venules are quite normal and not at all distended. It seems, indeed, that they may be smaller because they are not kept filled with blood. At any rate, it seems difficult to understand why increased blood pressure and long continued distension of the pulmonary circulation, as in mitral stenosis, should give rise to the moderate arteriosclerosis which is frequently observed there, unless it be that in the retarded passage of venous blood there may be opportunity for the deposition of lipoid substances in the arterial wall, with the arteriosclerotic changes that follow. If we lean to this idea it becomes especially difficult to explain the localisation of lipoidal substances in the pulmonary arteries alone in this case in which there was no obstruction to the circulation until the sclerosis produced it.

As for the rôle of syphilis in producing this change, the idea seems purely gratuitous. There are no histological changes suggestive of the true, fairly well known, syphilitic alterations of the pulmonary artery; there was no history of syphilis, the Wassermann test was negative, there were no gross or microscopic changes in any organ suggestive of syphilis. It may be said that in the exactly similar cases reported in the literature, no one has found spirochaetes except Arrilaga in one case, for the case ascribed to Warthin was a different condition—one of true syphilis with aneurysm—in his case of Ayerza's disease resembling this no spirochaetes were found by him.

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THE NEGATIVE EFFECT OF THE ADMINISTRATION OF LIVER IN HEMOPHILIA[1]

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The treatment of hemophilia by alteration of various dietary factors has often been attempted. The demonstration by Minot and Murphy (1) (2) of marked improvement in persons suffering from pernicious anemia during the administration of adequate amounts of liver has led to the use of this substance in other forms of blood disease.

Pickering (3) has reported beneficial results in hemophilia during the administration of liver. He describes pronounced decreases in coagulation times of the blood and definite improvement of symptoms in 3 cases.

The present communication concerns the effect of feeding raw beef liver to 4 hemophiliacs whose ages ranged between thirteen and twenty-three years. Each of these patients gave classical histories of hemophilia. They had had repeated hemorrhages into their joints, severe bleeding from injury, and the coagulation times of their blood were greatly prolonged.

The coagulation times of both venous and capillary blood were observed. The coagulation time of venous blood was determined by the method of Lee and White (4) and at the same time by the capillary tube method. The latter method was also used for capillary blood. Great care was taken to obtain venous blood without the admixture of tissue juices. One cubic centimeter of blood was placed in each of 4 test-tubes (inside diameter 8 mm.). Coagulation was considered complete when a tube could be inverted without disturbing its contents. The first tube was examined at five-minute intervals until coagulation had occurred. Consecutive tubes were then examined in the same manner. The coagulation time of the last tube was always the longest as that

[1] Submitted for publication June 1, 1931.

tube was disturbed least, and this was considered the true coagulation time. For the capillary tube method, glass tubes (inside diameter 1 mm.) were filled with venous blood from a test-tube or from a clean puncture wound of the finger when the clotting time of capillary blood was determined. Portions of the capillary tubes were broken at 1-minute intervals, and when a fibrin thread could be drawn out to a length of 2 cm., coagulation was considered complete. Determinations

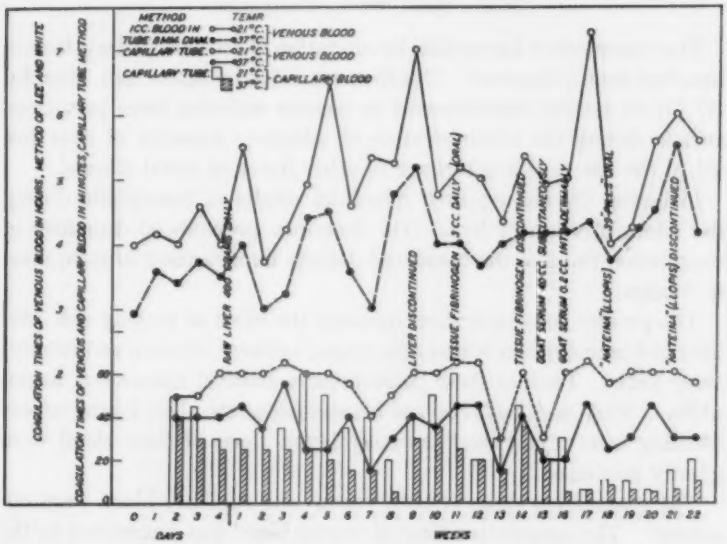

FIG. 1. THE COAGULATION TIMES OF VENOUS AND CAPILLARY BLOOD IN A CASE OF HEMOPHILIA DURING THE ADMINISTRATION OF LIVER, TISSUE FIBRINOGEN, GOAT SERUM, AND "NATEINA" (LLOPIS)

by both methods on both venous and capillary blood were made at 21°C. and at 37°C.

After control periods of at least four consecutive days, each of 3 patients ingested daily 400 grams of raw beef liver for sixty-three, seventy-three, and eighty-one days, respectively; and 1 patient, aged thirteen years, ingested 250 grams of raw beef liver per day for fifty-seven days.

No decrease in the coagulation times could be demonstrated during the administration of liver in any case. Typical results in one case are shown in figure 1. There was also no evidence of improvement of symptoms during this period. Hemorrhages into joints continued in all cases and gross hematuria occurred in one case. The fluctuations in coagulation times, as illustrated in figure 1, have been noted often in untreated cases of hemophilia.

The 3 cases reported by Pickering were apparently less severe than those reported here. In two of his patients liver feeding was begun shortly after severe hemorrhages. As the coagulation time of venous blood is often decreased after pronounced loss of blood, perhaps some of the decreases in the coagulation times noted in his cases were due to this circumstance.

As the administration of liver proved ineffective in the 4 cases studied, tissue fibrinogen, a substance derived from lung tissue and described by Mills (5), was then given orally to two of the hemophiliacs for 13 and 22 days, respectively. The coagulation times obtained after this material was fed to one of these patients are also shown in figure 1. There was no significant change in coagulation times nor improvement of symptoms.

Vines (6) has demonstrated a marked decrease in the coagulation time of capillary blood within two hours after the intradermal injection of animal serum in hemophiliacs previously sensitized to the serum. This observation has been confirmed by Mills (7). No determinations of the coagulation time of venous blood are recorded. Eley and Clifford (10) have extended similar observations to include both venous and capillary blood. They observed a very distinct decrease in the coagulation time of capillary blood but no change in that of venous blood.

The observations of Eley and Clifford were repeated in two of the patients described here. One was sensitized with goat serum and the other with horse serum and then after an appropriate interval of time each patient received an intradermal injection of the same serum with which he had been sensitized.[2] The coagulation times obtained in each case are recorded in figures 1 and 2 respectively. Very distinct

[2] A positive skin test was noted after the intradermal injection of serum in each case.

decreases in the coagulation times of capillary blood which persisted for more than twenty-one days were noted within two hours after the intradermal injection of serum. However, the coagulation times of venous blood were unaffected and there was no improvement of symptoms.

The use of food and preparations with high vitamin content has also been advocated in hemophilia. Among the most favorable reports of this form of therapy are those concerning the use of "Nateina"

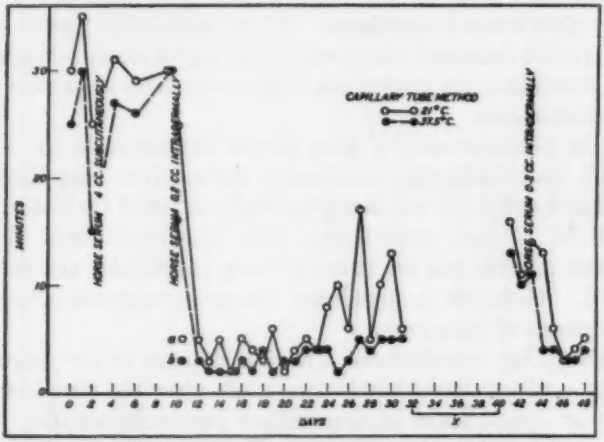
MINUTES
30
20
10
0
HORSE SERUM 4 CC SUBCUTANEOUSLY
HORSE SERUM 0.2 CC INTRADERMALLY
GOAT SERUM 0.2 CC INTRADERMALLY
CAPILLARY TUBE METHOD
37°C.
37.5°C.
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
DAYS
X
COAGULATION TIMES 4 HOURS AFTER INTRADERMAL INJECTION OF HORSE SERUM
X- PATIENT FAILED TO REPORT FOR OBSERVATION DURING THIS PERIOD

FIG. 2. THE COAGULATION TIMES OF CAPILLARY BLOOD IN A CASE OF HEMOPHILIA BEFORE AND AFTER THE ADMINISTRATION OF HORSE SERUM

(Llopis) (8) (9), a preparation which is said by its maker to be rich in vitamins A, B, C, and D. This substance was administered to one patient for twenty-one days without improvement of symptoms. Coagulation times during this period are shown in figure 1. Because the patient could not be kept indefinitely for observation, "Nateina" was given shortly after goat serum was administered. The decreases in the coagulation times of capillary blood present following the injection of goat serum and maintained while "Nateina" was fed are attributed to goat serum rather than to "Nateina." This is because

Vines (6) and Eley and Clifford (10), as well as the results shown in figure 2 indicate that the period of reduction of the capillary coagulation time after the use of animal serum exceeds the twenty-one-day period during which "Nateina" was given. No change in the coagulation times of the venous blood was noted.

SUMMARY

1. The daily oral administration of raw beef liver in large amounts for eight to eleven weeks to 4 patients with hemophilia produced no improvement of symptoms or significant changes in the coagulation times of venous or capillary blood. Similar negative results were noted during the oral administration of tissue fibrinogen (Mills) to two of these patients and "Nateina" (Llopis) to one of them.

2. The intradermal injection of animal serum in 2 patients, who had been sensitized previously to the serum, produced a prompt decrease in the coagulation time of capillary blood which persisted for more than twenty-one days. The coagulation time of the venous bloods was not affected. These observations confirm those of Eley and Clifford.

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BOOK REVIEWS

Tobacco. By WALTER L. MENDENHALL, M.D. Harvard Health Talks. 69 pp. (*Harvard University Press, Cambridge, 1930.*)

A popular lecture on the physiological and pathological effects of smoking. The material is presented in an interesting and readable form with the pros and cons both frankly stated. The conclusion reached is expressed in the following question and answer.

"Do its pleasures outweigh its possibilities of evil?

"That is for the individual to decide for himself."

W. H. H.

Traité de Biocolloïdologie. Par W. KOPACZEWSKI. T. I. FASC. II et III. Deuxième éd rev. 503 pp. Frcs. 60. (*Gauthier-Villars et Cie, Paris, 1930.*)

Fascicule II. Mesure des concentration moléculaires et ioniques.

Fascicule III. Mesures capillaires et électriques.

These two sections complete volume I of a projected five-volume treatise on colloids in relation to biolgy and medicine.

B. C.

The hair. Its Care, Diseases and Treatment. By W. J. O'DONOVAN, O.B.E., M.D. (Lond.), M.R.C.P. 218 pp. $3.50. (*P. Blakiston's Son and Company, Inc., Philadelphia, 1930.*)

This small volume of 211 pages gives an excellent description of the hair and its diseases. After brief introductory chapters upon the structure and development of the hairs and the hair follicles the various diseases are considered with reference to their etiology and treatment. The terminology, as in the case of the skin-diseases, is rather formidable. There is an interesting chapter upon the public health aspects of the subject, with especial reference to the regulations to be enforced in barber-shops. Another chapter deals with hair-dyes and the dermatitis that may result from their use. The book is written simply, almost sketchily, but the author evidently knows his subject well. One could wish that something more had been said in regard to the physiology of hair, especially in regard to the conditions influencing its growth, but doubtless there is little known upon this side of the subject.

W. H. W.

Personal and Community Health. By CLAIR ELSMERE TURNER, M.A., D.P.H. Third edition. 443 pp. $2.75. (*C. V. Mosby Company, St. Louis, 1930.*)

As stated in the preface, this book is designed to meet the needs of students in normal schools, professional schools, Colleges and Universities, in the subjects

of personal hygiene and public health. It is divided, therefore, into two parts, one dealing with personal, the other with community health. The latter is the larger half. It takes up in an informing way a great variety of topics including the organization and administration of our federal and local health departments. The treatment, of necessity, is somewhat general and fitted to the needs of the reader for general information rather to those of the special student. The author attempts from time to time to supply scientific explanations, but since his readers are presumably lacking in technical training, it is questionable how much good such efforts accomplish. One wonders, for example, what kind of an impression his description of Ehrlich's side-chain theory of immunity, with its accompanying graphic illustrations of antitoxins, agglutinins, amboceptors, haptophore and zymophore groups, makes upon the untrained reader.

The part upon personal hygiene is less satisfactory. It shows the usual faults of elementary treatises upon this important but unfortunate subject. There is a large amount of exhortation, in the *argumentum ad hominem* style, which is tiresome and probably futile. One could wish that writers of textbooks on this subject would content themselves with a simple presentation of facts, as is the custom with textbooks on other scientific subjects, instead of adopting the method of the religious tract. There are also some of the usual unwarranted statements that have come own to us by tradition or that reflect the current fashions in medicine, such as the supposed evils of autointoxication from the alimentary canal or the virtues of water drinking in excess. The compass of such books forbids critical discussion and necessitates brief positive statements, but for that very reason great care should be shown in the selection of the advice passed on to the trusting reader.

W. H. H.

Burns. Types, Pathology and Management. By GEORGE T. PACK and A. HOBSON DAVIS. x + 364 pp. (*J. B. Lippincott, Philadelphia and London.*)

Beginning with an historical account, which is a little too short, the authors in the first part of their volume deal successively with the etiology, incidence, classification, local and general tissue changes, symptoms, diagnosis, complications, prognosis, and cause of death from burns. The second part of the book describes the management of thermal burns and discusses such methods of treatment as the wet dressings, natural and artificial sunlight, occlusive dressings utilizing paraffin, oils, and similar substances, and the excision of the burned tissue. The authors also deal briefly with skin grafting, diseases of burn cicatrices, and deformities from burns. The third part of the volume is devoted to regional burns and to burns by such specific agents as electricity, lightning, the Rontgen ray, radium, the sun, chemicals, and war gases.

Possibly one might take exception to the brief manner in which the plastic surgical procedures have been given, and look in vain for a discussion of some of the combination methods, such as artificial light and gentian violet. Certainly the microphotographs leave much to be desired, and it is hoped that in the subsequent

editions, which this volume deserves, the publishers will improve this feature so that the illustrations will conform to the high standard of the text. The authors are fully appreciative of the slight progress made in the management of burns, and it is refreshing to have them bring in the quotation of another surgeon to the effect that if the mummy of Rameses II should ever be reanimated, he would realize that the treatment of burns had also slept during the centuries. In short, the book is very interesting, useful and readable, and can be unhesitatingly recommended to the profession.

F. C. L.

Travaux de L'Institut de Sérologie de Bucarest. Edited by Dr. J. Cantacuzène. Collected papers from the Archives Roumaines de Pathologie Expérimentale de Microbiologie and Comptes Rendus des Séances de la Société de Biologie. Société Roumaine de Biologie, Bucarest, 1928.

The researches of this institute, like those of the Pasteur Institute in Paris, are essentially bacteriological and immunological in character. Founded in 1901 at Bucarest by Jean Cantacuzène, the institute has had from the beginning a group of men well known for their researches. The organ for the publication of most of their work at present is the *Archives Roumaines de Pathologie Expérimentale et de Microbiologie*, which issued its first volume in 1928. The collected papers cover a wide range of investigation, such as immunity reactions of invertebrates, the effect of hydrogen-ion concentration on diphtheria and dysentery toxins, types of meningococci in Roumania, filterable forms of the tubercle bacillus, pathological and immunological reactions of guinea-pigs to tuberculosis, vaccination against tuberculosis with BCG, infection and immunity with anthrax, and studies on anaphylaxis. Many of the articles have excellent plates and illustrations.

G. H. B.

The Chemical Aspects of Immunity. By H. Gideon Wells, Ph.D., M.D. Second (Revised and Enlarged) Edition. Pp. 286, with 3 illustrations. Cloth $6.00. (*The Chemical Catalog Company, New York, 1929.*)

As in all of the biological sciences, progress in our knowledge of immunity, or the processes by which living creatures defend themselves against injury, is becoming more and more dependent on the principlesof chemistry. The science of immunology was built on the fundamental theories of Ehrlich, Metchnikoff and Bordet, which are essentially biological theories. A more satisfactory interpretation of many of the phenomena of immunity has been given during the past few years by the progress in the physics and chemistry of living matter. There had accumulated in the literature numerous articles which had not been coördinated and are not readily accessible. Dr. Wells has brought together in his book in well organized form a large number of the most important of these investigations. They include such subjects as the chemical aspects of antigens, toxins, antibodies, specificity, neutralization of toxin by antitoxin, the mechanism of agglutination and precipitation, complement fixation, the Wassermann reaction, anaphylaxis,

cellular immunity, and the resistance to non-antigenic poisons. Of special interest is the newer knowledge of the so-called "haptenes." The book has an excellent bibliography, and, as has already been demonstrated by the first edition, should be of great aid to research workers and others interested in the subject.

G. H. B.

Applied Physiology. By SAMSON WRIGHT, M.D., M.R.C.P. With Introduction by Swale Vincent, M.D., LL.D., D.Sc., F.R.S. (Ed. and Canada). Third edition. 552 pp. (*Oxford Medical Publication, Oxford University Press, London, 1929.*)

A third edition of Wright's "Applied Physiology" has been published. Although written for the advanced medical student and for the practitioner who wishes to obtain a review of the advances in physiology and their clinical application, some of the chapters, especially that on the nervous system, cover the subject better than the standard textbooks in physiology and so the book recommends itself to the beginning as well as to the more advanced student.

This edition is a thorough revision of the former; the newer knowledge of nerve metabolism, tissue respiration, conditioned reflexes and other subjects have been added. Although the immediate application of physiology to medicine is not always apparent, some of these advances may be of importance in the future. This book does give a better review of present day physiology than of its applications to medicine.

C. L. G.

Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus. By WILLIAM HARVEY, M.D. An English Translation with Annotations by Chauncey D. Leake. Second edition. 150 pp. $.90. (*Charles C. Thomas, Publisher, Springfield, 1931.*)

Three hundred years after the publication of Harvey's famous book "De Motu Cordis" three new editions appeared, from the Nonesuch Press, London, from Lier and Co., Florence, and from Charles Thomas, Springfield, Ohio. The edition published by Thomas presented a fascimile copy of the original Latin edition and a new English translation by Leake. A second edition of this book has been published, giving only the Leake translation. Bound in paper, retaining all the plates of the first edition, this second edition is sold primarily for the use of medical students, at a very low price, a trend that should be encouraged among publishers of medical books.

The Leake translation attempts to present Harvey's thought in present day physiological manner. In order to bring out the full significance of Harvey's work with reference to present knowledge, footnotes have been added which gives the book added interest.

No better account of the physiological method of approach to a problem can be found than in Harvey's "De Motu Cordis." Making a study of the motion of the heart and blood from the comparative and embryological standpoints, and using

quantitative methods of experimentation, Harvey discovered the circulation of the blood and founded modern physiology. Now that a good English translation is available, this classic should be read by everyone interested in biological sciences, for it does illustrate what Osler termed "The Growth of Truth."

C. L. G.

Gynaecology for Nurses and Gynaecological Nursing. By COMYNS BERKELEY, M.A., M.D., M.C. Cantab., F.R.C.P. (Lond.), F.R.C.S. (Eng.). Revised and Enlarged. 426 pp. $2.75. (*G. P. Putman's Sons, New York, 1930.*)

From the fact that each hospital has its own particular method of teaching nurses to care for gynaecological patients, it becomes a painstaking task to prepare an adequate book on gynaecology and gynaecological nursing.

Berkeley has incorporated surgical bacteriology, pathology and symptomatology —subjects of paramount importance. Much space has been given to sterile dressings, sterile tables, instruments, including names, etc. The nurse can thus become familiar with these before she undertakes the work of the operating-room.

Surgery has made such active strides in the past few years that more knowledge on the part of the nurse is now demanded. The author has kept in mind that, in order to render the surgeon efficient assistance, the nurse must understand the principles upon which he is working.

Emergencies, which most nurses have difficulty in meeting, are thoroughly emphasized and explained. The various surgical methods and after-treatment are subject to modification, depending on the individual patient, but the author has given in detail practical, useful and excellent general information which will be of help in all hospitals.

This book will assist in promoting better work, will facilitate the labors of the nurse and add to the satisfaction and comfort of patients, as well as expedite service to the surgeon.

O. D. C.

Warren's Handbook of Anatomy, from original dissections by John Warren, M.D., text by Robert M. Green, M.D., drawings by H. L. Aitken. pp. 384. (*Harvard University Press, Cambridge, Mass., 1930.*)

A review of this Handbook of Anatomy, which bears Dr. Warren's name, must, in the nature of such work, remain scarcely more than a personal impression. The work has to be seen to be appraised, since its raison d'être is the large series of dissections made by Dr. Warren, and their superb portrayals by Mr. H. F. Aitken. If elsewhere in this country there has appeared a collection of gross anatomical material as comprehensive as this, and as successfully illustrated, the present reviewer is unaware of it.

The arrangement of the illustrations and text suggests a regional or topographical treatise, for which, indeed, as the preface states, the dissections were originally prepared. Such an arrangement should in many ways be gratifying to the student,

who is faced with the practical problems of dissevering for himself the multitudinous parts of the human body.

In the sections dealing with the extremities the skeletal elements and the joints are first depicted, and then the systems of muscles are applied to them, much after the fashion of Leonardo da Vinci's red crayon drawings, of which Vasari says, "He did the skeleton, adding all the nerves and muscles." Unhappily, in the Warren sequence, the muscles alone, and not the nerves, are added. A few pages of text at the end of the sections deal with the great nerves of the upper extremity and with the sacrococcygeal plexus; but these and the running text-comment on specific nerves are certainly not enough to inform the student of his findings on the cadaver. The blood-vessels of the extremities are portrayed only in piecemeal, and the lymphatics are accorded but a brief text-treatment. The inclusion of vessels and nerves as a continuum in proper relation with muscles and skeleton would have entailed no great extension of the book, and would have made good a serious lapse. The vessels and nerves of the head and trunk are extensively and beautifully figured.

The text, begun by Dr. Warren and completed by Dr. Green, is very lucid and concise, with a brief comment now and again of some functional, or developmental, or practical significance. The chapter entitled, "The Abdominal Cavity," is introduced by an exceptionally good account of the development of the peritoneum; although the simple and highly useful schemata, in terms of which we customarily think of the gastro-intestinal and peritoneal evolvements, are unfortunately lacking.

As an atlas for use by the surgeon and general practitioner, the Warren Handbook is doubtless one of the best. But because of the omissions noted above, and in general because of the absence of diagrams, one cannot quite concur in the editor's belief that the book meets the needs of a first-year course in human anatomy. In the first place, the student needs more than one textbook of anatomy, just as he needs more than one cadaver, if for no other reason than to impart to him the sense of diversity. In the second place, his curiosity often extends, as legitimately it should, beyond the static conception of anatomy, exemplified in the handbook and the cadaver, to the human body as a highly integrated, working organism, whose ways and means are the ultimate desideratum of anatomy as a biological science.

C. F. DEG.